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Patent  
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PCT/GB 99/02620  
63236  
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The Patent Office  
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Cardiff Road  
Newport  
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NP10 8QQ

GB99/2620

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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Signed *Andrew Gersey*

Dated 5 November 1999

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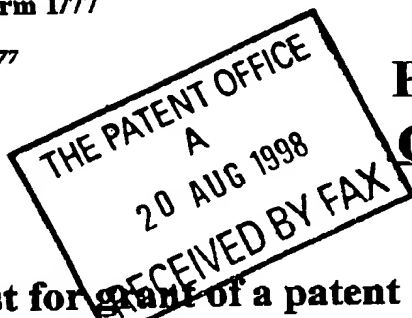
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# The Patent Office

# 1/77

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P01/7700 25.00 - 9818156.3

The Patent Office

Cardiff Road  
Newport  
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## Request for grant of a patent

(see the notes on the back of this form. You can also get  
an explanatory leaflet from the Patent Office to help  
you fill in this form)

1. Your reference PBA/D088221PGB

2. Patent application number  
(The Patent Office will fill in this part)

**9818156.3**

3. Full name, address and postcode of the or of  
each applicant (underline all surnames)

THERAMARK LIMITED  
90 FETTER LANE  
LONDON  
EC4A 1JP

Patents ADP number (if you know it)

07497514001  
UNITED KINGDOM

If the applicant is a corporate body, give the  
country/state of its incorporation

4. Title of the invention DRUG TARGETING III

5. Name of your agent (if you have one)

Marks & Clerk

"Address for service" in the United Kingdom  
to which all correspondence should be sent  
(including the postcode)

Sussex House  
83-85 Mosley Street  
Manchester  
M2 3LG

Patents ADP number (if you know it)

18004

6. If you are declaring priority from one or more  
earlier patent applications, give the country  
and the date of filing of the or of each of these  
earlier applications and (if you know it) the or  
each application number

Country	Priority application number (if you know it)	Date of filing (day/month/year)
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7. If this application is divided or otherwise  
derived from an earlier UK application,  
give the number and the filing date of  
the earlier application

Number of earlier application	Date of filing (day/month/year)
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8. Is a statement of Inventorship and of right  
to grant of a patent required in support of  
this request? (Answer 'Yes' if:  
a) any applicant named in part 3 is not an inventor, or  
b) there is an inventor who is not named as an applicant, or  
c) any named applicant is a corporate body.  
See note (d))

YES

## Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form  
Description 2  
Claim(s) -  
Abstract -  
Drawing(s) -

THE PATENT OFFICE  
20 AUG 1998  
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10. If you are also filing any of the following, state how many against each item.

Priority documents -  
Translations of priority documents -  
Statement of Inventorship and right to grant of a patent (*Patents Form 7/77*) -  
Request for preliminary examination and search (*Patents Form 9/77*) -  
Request for substantive examination (*Patents Form 10/77*) -  
Any other documents -  
(Please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

MARKS & CLERK

Date

20/08/98

12. Name and daytime telephone number of person to contact in the United Kingdom

MR. P.B. ATKINSON - 0161 236 2275

### Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

### Notes

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- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

### DRUG TARGETING III

The present invention relates to bioreductive drug conjugates for use in targeting of therapeutic agents to localised regions of hypoxic and/or ischemic tissue within the body.

This application is supplemental to our copending U.K. patent applications filed 19th August 1998 entitled Drug Targeting I and Drug Targeting II.

According to a first aspect of the present invention we provide bioreductive conjugates per se comprising bioreductive moieties as disclosed in either of the aforementioned applications and a therapeutic agent as specifically disclosed in either application.

Thus, in accordance with the present invention, we provide per se protection for bioreductive conjugates incorporating therapeutic agents as disclosed in the aforementioned applications. These conjugates of the first aspect of the invention may be used for the particular therapeutic application for which they are disclosed in the aforementioned applications, or as appropriate for any other therapeutic application as disclosed in the aforementioned applications, or as appropriate for any other therapeutic application.

In accordance with a second aspect of the present invention there is provided bioreductive conjugates comprising a bioreductive moiety as disclosed in either of the aforementioned applications in conjunction with a therapeutic agent which is selected from immunosuppressives, cell cycle specific drugs, cell cycle non-specific drugs, metalloprotease inhibitors and inhibitors of nitric oxide synthase.

The conjugates of this second aspect may be used as appropriate for any therapeutic application as disclosed in the aforementioned applications, or as appropriate for any other therapeutic application.

In the case where the therapeutic agent is an immunosuppressive, the bio-reductive conjugate may be used in transplant surgery. The immunosuppressive may, for example, be cyclosporin A.

Examples of cell cycle specific and cell cycle non-specific drugs include hormones and hormone analogues, anti-angiogenic, (e.g. endostatin, angiostatin), vascular targeted drugs (e.g. combreastatin), metalloprotease inhibitors.

The treatment of periodontitis as contemplated in either of the aforementioned applications may be effected using a bio-reductive conjugate for which the therapeutic agent is a metalloprotease inhibitor.

The treatment of sepsis as contemplated in either of the aforementioned applications may be effected with an inhibitor of nitric oxide synthase.